ABSTRACT

Cellular surface receptors exist in an equilibrium between an inactive and an active state. To date, prior art approaches to studying receptor function and screening receptors for new drugs focused on first identifying the endogenous ligand for the receptor (or a synthetic substitute) and then identifying antagonists to the receptor existing in an inactive structural conformation. It has now been recognized that very valuable information relevant to treatment of diseases caused by receptors can be directly obtained by identifying compounds which act as inverse agonists to constitutively activated forms of the receptor; i.e., those in which the equilibrium has been shifted towards the active state. Methods to constitutively activate receptors are used to specify the genetic information coding for receptors which are then expressed in appropriate expression systems. Assays which measure the cellular response elicited by compounds acting on the receptors can identify both inverse agonists and agonists of the receptor. High throughput screening may be used to rapidly identify these compounds. A particularly relevant feature is that modulators of receptor action can be identified with no prior knowledge of the endogenous ligand or receptor function. The method of the invention is particularly applicable to orphan receptors.